

**RESPONSE**

1. Claims 15, 16 and 31 – 39 are cancelled from the application, as they should have been in the last action. Examiner is thanked for the correction, and for allowing it to be made at this point.

The claims newly added in the last response, claims 40 - 48, are believed by applicant to read on the elected invention.

Claims 2-14, 17-30, and 40-48 have been amended to correct the misspelling of "biocompatible" to the correct "biocompatible", or to insert "biocompatible" in place of "surgical". Claim 1 and many of the other claims have been amended, in almost all cases for improvement of clarity without intent to alter the scope of such claims. Only the following claims have been amended with the intent to narrow their scope: Claim 1, in the last response; and in this response, claim 28 and claim 40.

2. Sect. 112 corrections to the claims:

Claims 1-14, 17-30, and 40-48 were rejected under sect. 112 as being indefinite. The following response to this rejection is a combination of explanation and amendments, as appropriate. A complete set of claims as now pending is above. It is believed that the indefiniteness of each of these claims has been removed by amendment and/or explanation.

a. Claim 1: The objection is that the statement "wherein the polyol being terminated with at least one polyisocyanate in solution with at least (N-1)% of said solution" is unclear. The claim has been amended, solely for improving the ease of understanding it, by adding ", said terminated polyol being" after the first "isocyanate", and replacing "being" with "is", "with" with "wherein", "comprising" with "comprises", and adding an "and" and an "about". The claim is believed to now be clear.

The "N" is the same number in "N" and in "N-1", so that a solution with, for example, an average functionality (N) of 2.5, would have at least (N-1)%, i.e., 1.5% by weight of the entire solution, as "free" molecules of unreacted low molecular weight polyisocyanate, for example toluene di-isocyanate (TDI) or isophorone di-isocyanate (IPDI).

If more discussion is needed, useful background is on p. 26 of the specification, after example 7. The polymer is described as a "polyol", implying that the functional groups are hydroxyl groups. As described in the Examples, the polyol is treated with an excess of a polyisocyanate, usually a di-isocyanate. In example 7, for example, N is 3 (the polyol is trifunctional), the polyisocyanate is a di-isocyanate, (N-1)% is 2%, and the actual free isocyanate content is 3.1%, which is greater than 2%.

b. In claim 17, now independent, similar amendments are made, and elsewhere as needed.

c. "Molecular number" in claims 19 and 22 is used in the specification, for example on p. 28. What is intended by this phrase could be rephrased as the "number of molecules". The claims have been amended to reflect this, solely for clarification.

d. Claims 23, 47: "water reactivity". Relative reactivity, or reaction rate, of the isocyanate group with water is meant. The best discussion is on p. 20 -24 of the specification, where it is noted that there are different reaction rates of isocyanates depending on the backbone to which they are attached, and on p. 27. The "R1" and "R2" notation is introduced on p. 28-29. The claims have been amended to clarify that the rate referred to is the "rate of reaction with water". It is believed that this will eliminate any impression of vagueness, without changing the scope of the claim.

e.) Claims 23, 24 and 47: Yes, each of the polyols has from 1.5 to 8 functional groups. The phrase "of functionality" has been replaced with "having an average [[of]] functionality of", which should clarify the meaning without any change of scope.

f) In claim 24, a comma has been added to make the phrase read, "...being in solution solution, wherein ...". It is believed that this will remove any ambiguity.

g) Claim 28: "stiochiometric". Claim 28 is amended. The phrase is found in the specification on p. 29 beginning on line 11 (or alternatively, as the last 15 lines or so of

paragraph 0066). What was meant was that preferably, there is enough of the slow reacting isocyanate on the polymer to quench any leftover amine, etc groups caused by reaction of the faster-reacting isocyanates in solution and/or on polymers. This is accomplished by stoichiometric ("having the same functional number of ") equivalence of the two types of reactive isocyanate groups.

3. (p. 4) Claims 44, 45, 46:

-in each of these claims, the word "surgical", is replaced by "biocompatible", "organic" is replaced by "polymeric", and the relationship between "unreacted" polyisocyanate, in the preamble, and "free" in the process steps, is clarified. In some places, commas are added with the intent of making the phrases easier to read.

The polymerization sequence, which is meant to distinguish the way the adhesive reacts, is now presented in these claims as a characterization of the composition. For example, in claims 44, 45 and 46 the preamble now reads

" wherein the adhesive is characterized in having a reactivity such that"...

It is believed that this change properly presents these claims as composition claims. Otherwise, no change in scope is intended.

p5: claim 48: yes, dependence on claim 47 was meant.

### **Rejections under 35 USC Sect. 102**

Claims 1, 2, 3 and 8 are again rejected as anticipated by Muller et al US 5,624,972. Claim 1 was amended in the last response to require at least 70% EO (ethylene oxide) monomer content. The claim also has the limitation of at least (N-1) % of free isocyanate in the final composition, before application to the patient (and concomitant crosslinking. Further amendments have been made to the claims to clarify them.

It appears that the difference between Muller's materials and those of applicants is not clear. In brief, the difference between the prepolymers of applicants, and the prepolymers or finished products of Muller et al, is that applicant's products are

hydrophilic, and Muller et al's are hydrophobic. Moreover, each product is necessarily hydrophobic or hydrophilic in order to function, and it would be obvious to a person knowledgeable in the properties of the common polyether polyols that the one is not a substitute for the other.

It might be useful, in considering the differences between these claims and Mueller et al's materials, to review the differences between PEO polymers and PPO polymers, and the differing properties of their copolymers. In the PEO/PPO system, small changes in composition can cause large changes in the properties of the polymers. PEO or PEG is highly soluble in water, and is miscible with water in essentially any proportion. In contrast, pure PPO is insoluble in water, and it does not hydrate significantly. The copolymers ("PE/PO") of "PE" (EO) and PO, which at low molecular weights are used in the art as surfactants, tend to associate, when in aqueous solution, via their propylene oxide units, especially if present as blocks. On the other hand, the copolymers tend to hydrate, or to dissolve in water, to the extent that the copolymer contains ethylene oxide groups.

What applicants have found is that the range of about 5% or 10% to about 30% of PO (by number) in a copolymer with the rest of the units being EO, and after end-capping with a small di-isocyanate, there is enough association to give strength to the material after polymerization, but there is still enough EO, even after adding hydrophobic isocyanate groups, to allow miscibility of the polymers of the invention with water, and hence swelling will occur to a controllable extent after polymerization in the body. In particular, applicants' material does not precipitate out of solution when applied to tissue, while the activated polymers of Mueller et al, at least as described in an enabling way in their examples, would be expected to do so.

In contrast, as noted in applicant's response to the previous office action, Mueller et al use hydrophobic polyethers (dominated by propylene oxide monomers). This makes sense for an industrial foam, where absorption of water by the polyether molecules would be detrimental to the strength of the product. And in fact, it is readily observed that

commercial polyurethane foam is hydrophobic (water repellent), although water can be pushed into the pores. (And that is why kitchen sponges are made of more hydrophilic cellulosic derivatives!)

This concern is clearly expressed in applicant's specification. For example, on p. 19 it is noted that commercial prepolymers are called "hydrophilic" even if they can only incorporate 10% of water, or less. Consequently (second paragraph), "the majority of "hydrophilic" polyether polyols can be excluded for use in the present invention. In particular, the polyol of choice is a trifunctional form of PE/PO [i.e., P(EO/PO)] block polymer. The ration of PE [polyethylene oxide, as used here] to PO [here propylene oxide] is critical to the formation of the hydrogel. The PE provides the necessary hydrophilic nature, and the PO provides hydrogel strength."

Observations, based on experiments actually performed, are then offered: that pure PE swells rapidly and dissolves, while copolymers with greater than 30% of PO will not absorb enough water. A range of about 10 to 30% of PO subunits is clearly preferred. All of the examples are in this range. (With hindsight, it would have been of interest to have written up some of the failed experiments as Examples, as well as selected successful ones.)

The range of suitable materials is thus strongly constrained in the specification, as is reflected in the claims (particularly as amended) and does not overlap the range of materials useful in Muller, precisely because Muller's end application requires non-hydrophilic materials. One skilled in the art would not find Mueller et al's materials suitable for making applicants' product, and conversely applicant's materials would not be thought or found suitable in Mueller et al's product.

It is therefore believed that claim 1, as amended, is clear and is distinguished over Muller et al. Likewise, dependent claims 2, 3 and 8 are likewise distinguished over Mueller et al. Withdrawal of the rejection of these claims under Sect. 102 is respectfully requested.

**Rejections under 35 USC sect. 103**

6, 7 The other claims (4-7, 9-14, 17-30, 40-48) are rejected as being obvious in light of Muller. The arguments presented are respectfully traversed, under the reasoning presented in the above discussion. Claim 1 was amended in the previous response to specify that the ethylene oxide monomer content is at least about 70%. This amendment is maintained in the presently-presented claims. Applicant believes that the limitation in claim 1 to 70% ethylene oxide monomers in the polyol is distinctive.

The material on pp 19 - 23 of the specification presents the results of applicant's experience in early stages of the project. Applicant is completely clear that only compositions containing at least about 70% EtO units are suitable for making tissue adhesives. While the material in this section is not presented in the form of examples, it is certainly unambiguous.

For the same reason, the compositions described in independent claim 17, a two-copolymer composition with one copolymer having 10 - 30% PO, and the other having less than about 10% PO - are neither presented in Muller, nor is there anything in Muller which would motivate a person to try such compositions (70 - 90+ % EtO), since they are known in the industrial field to be not useful for making a conventional polyurethane foam.

In summary, it appears to applicants that the reasons for rejection that have been presented are not, when the technical background is understood, properly applicable to the claims as amended. Passage of the claims to issue is respectfully requested.

If a discussion would be helpful in coming to agreement on the patentability of the present claims as amended, applicant's registered practitioner can be reached at 978-790-7186 during business hours M-F (8 - 5) and 7- 9 PM most weekday evenings, or by e-mail at fckirk@comcast.net.



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